CARFDEXALENA Regimen
Carfilzomib, Dexamethasone, Lenalidomide

**Disease Site**  
Hematologic - Multiple Myeloma

**Intent**  
Palliative

**Regimen Category**  
Evidence-Informed:
Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

**Rationale and Uses**  
For the treatment of patients with relapsed multiple myeloma, with good performance status and adequate renal function, who have received at least 1 prior treatment.

Refer to NDFP form for details on other funding criteria, especially for patients who were previously on lenalidomide-based or bortezomib-based treatments.

**Supplementary Public Funding**
- [carfilzomib](#)
  New Drug Funding Program (Carfilzomib (Triplet Therapy) - In Combination with Lenalidomide and Dexamethasone for Relapsed Multiple Myeloma)  
  (Funded by NDFP for up to 18 cycles)

- [dexamethasone](#)
  ODB - General Benefit (dexamethasone) (tablets)
lenalidomide
Exceptional Access Program (lenalidomide)
B - Drug Regimen

Cycle 1:

- **carfilzomib** 20 mg /m² IV Days 1, 2
- **carfilzomib** 27 mg /m² IV Days 8, 9, 15, 16
- **dexamethasone** 40* mg /day IV / PO Days 1, 8, 15, 22
- **lenalidomide** 25** mg /day PO Days 1 to 21

Cycles 2 to 12:

- **carfilzomib** 27 mg /m² IV Days 1, 2, 8, 9, 15, 16
- **dexamethasone** 40* mg /day IV / PO Days 1, 8, 15, 22
- **lenalidomide** 25** mg /day PO Days 1 to 21

Cycles 13 to 18#:

- **carfilzomib** 27 mg /m² IV Days 1, 2, 15, 16
- **dexamethasone** 40* mg /day IV / PO Days 1, 8, 15, 22
- **lenalidomide** 25** mg /day PO Days 1 to 21

Cycle 19 onwards# Report as regimen code DEXALENA:

- **dexamethasone** 40* mg /day IV / PO Days 1, 8, 15, 22
  (*Outpatient prescription in 4 mg tablets for patients on PO route)
- **lenalidomide** 25** mg /day PO Days 1 to 21
  (**Outpatient prescription in 5 mg, 10 mg, 15 mg or 25 mg capsules)
Lenalidomide may only be prescribed and dispensed by physicians and pharmacists registered with RevAid®. Patients must also be registered and meet all conditions of the RevAid® program.

C - Cycle Frequency

REPEAT EVERY 28 DAYS

Unless disease progression or unacceptable toxicity occurs.

D - Premedication and Supportive Measures

**Antiemetic Regimen:** Low

**Other Supportive Care:**

Also refer to CCO Antiemetic Summary

**Lenalidomide:**
- Patients must also be registered and meet all conditions of the RevAid program, including contraception.
- Careful consideration and monitoring must be taken with erythropoietin stimulating agents (ESAs), since the concomitant use of ESAs with lenalidomide may potentiate the risk of thrombosis.

**Carfilzomib:**
- Consider the use of antiviral prophylaxis during carfilzomib therapy to decrease the risk of herpes zoster reactivation.
- The use of thromboprophylaxis is recommended in patients being treated with carfilzomib in combination with lenalidomide and dexamethasone, with the choice of agent being based on patient risk factors and clinical status. Thromboprophylaxis should be continued for the duration of treatment with lenalidomide.
- Prophylaxis for tumour lysis syndrome in patients with high bulk disease.
- Adequate hydration is required prior to dosing in cycle 1, especially in patients at high risk for tumour lysis syndrome or renal toxicity.
Cycle 1:
- oral fluids (30 mL/kg/day for 48 hours before start of cycle)
- 250-500 mL of IV fluid before each dose and after (if needed)
Subsequent cycles:
- continue oral and/or IV hydration as needed

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered. Patients with a body surface area (BSA) > 2.2 m$^2$ should be dosed based on a maximum BSA of 2.2 m$^2$. Dose adjustments for carfilzomib do not need to be made for weight changes ≤ 20%.

**Dosage with toxicity**

**Dose levels**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Carfilzomib (mg/m$^2$)</th>
<th>Lenalidomide (mg)</th>
<th>Dexamethasone (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>27</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>-1</td>
<td>20</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>-2</td>
<td>15</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>-3</td>
<td>Discontinue if further reduction indicated</td>
<td>5</td>
<td>Discontinue if further reduction indicated</td>
</tr>
</tbody>
</table>
### Hematologic toxicity

<table>
<thead>
<tr>
<th>Toxicity (counts x $10^9$/L)</th>
<th>Carfilzomib</th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
</table>
| 1<sup>st</sup> instance: platelets < 30* | If platelets 10-30 without evidence of bleeding, maintain full dose.  
If evidence of bleeding or platelets < 10, hold until platelets ≥ 10 and/or bleeding is controlled, then resume at one dose level reduction. | Hold until platelets ≥ 30, then resume at one dose level reduction. | No change |

| Subsequent instances: platelets < 30* | If platelets 10-30 without evidence of bleeding, maintain full dose.  
If evidence of bleeding or platelets < 10, hold until platelets ≥ 10 and/or bleeding is controlled, then resume at one dose level reduction. | Hold until platelets ≥ 30, then resume at one further dose level reduction. | No change |

| 1<sup>st</sup> instance: ANC < 1 | If ANC 0.5-1, continue at full dose.  
If ANC < 0.5, hold until ANC ≥ 0.5, then resume at full dose. | Hold, add G-CSF, and resume at full dose when ANC ≥ 1 | No change |

| Subsequent instances: ANC < 1 | If ANC 0.5-1, continue at full dose.  
If ANC < 0.5, hold until ANC ≥ 0.5, then resume at one dose level reduction. | Hold, add G-CSF, and resume at one dose level reduction when ANC ≥ 1 | No change |

*A lower threshold of 20 x $10^9$/L may be considered for lenalidomide dose reductions for patients with myeloma involvement in the bone marrow > 50%*
<table>
<thead>
<tr>
<th>Non-hematologic toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxicity</strong></td>
</tr>
<tr>
<td>Any ≥ grade 3 non-hematologic toxicity(^1,2)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Edema &gt; grade 3 (limiting function and unresponsive to therapy or anasarca)</td>
</tr>
<tr>
<td>Muscle weakness &gt; grade 2</td>
</tr>
<tr>
<td>Exfoliative rash ≥ grade 2, SJS, TEN</td>
</tr>
<tr>
<td>Grade 3 or 4 cardiac events</td>
</tr>
<tr>
<td>Hypertensive crisis/emergency</td>
</tr>
<tr>
<td>Condition</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ARDS, ILD, pneumonitis, pulmonary hypertension, grade 3 or 4 dyspnea</td>
</tr>
<tr>
<td>Thrombotic microangiopathy (including TTP/HUS)</td>
</tr>
<tr>
<td>PRES</td>
</tr>
<tr>
<td>Increased LFTs</td>
</tr>
</tbody>
</table>

1In the event of possible drug-related non-hematologic toxicity, the physician should determine causality to the affected agent(s) and the recommended action(s) for each should be instituted.

2 Carfilzomib, lenalidomide and dexamethasone do not need to be held in the following cases: grade 3 nausea, vomiting or diarrhea (unless persisting more than 3 days with adequate treatment of antiemetics or antidiarrheals); grade 3 dexamethasone-related hyperglycemia; grade 3 fatigue (unless persisting for > 14 days). *discontinue in patients receiving 15 mg/m²

**Renal toxicity during treatment**

<table>
<thead>
<tr>
<th>Carfilzomib</th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine ≥ 2 x baseline, or CrCl &lt; 15 mL/min (or CrCl decreases to ≤ 50% of baseline) or need for dialysis: Hold and resume at one dose level reduction when renal function has recovered to within 25% of baseline. If tolerated, the reduced dose may be increased to the previous dose.</td>
<td>Hold until CrCl recovers to baseline, then resume at one dose level reduction. If recurs, reduce dose to 15 mg q 48 hours. If dialysis required, reduce dose to 5 mg once daily and administer after dialysis.</td>
<td>No change</td>
</tr>
</tbody>
</table>

Any use of the information is subject, at all times, to CCO’s Terms and Conditions.
**Hepatic Impairment**

<table>
<thead>
<tr>
<th>Carfilzomib</th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>The safety, efficacy and pharmacokinetics of carfilzomib in patients with hepatic impairment (ALT or AST ≥ 3 x ULN and bilirubin ≥ 2 x ULN) have not been studied.</td>
<td>Population pharmacokinetics suggest no dosage adjustment is necessary in mild hepatic impairment (total bilirubin &gt; 1 to &lt; 1.5 x ULN or AST &gt; ULN). No data available for moderate to severe hepatic impairment.</td>
<td>No adjustment required.</td>
</tr>
</tbody>
</table>

**Renal Impairment**

*Pre-existing renal impairment*

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Carfilzomib</th>
<th>Lenalidomide</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50</td>
<td>No adjustment required with pre-existing renal impairment at baseline, including those on dialysis.*</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>30 to 49</td>
<td>Reduce dose to 10 mg daily</td>
<td>Reduce dose to 15 mg q 48 hours.</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>For patients on dialysis receiving carfilzomib, the dose is to be give post-dialysis.</td>
<td>If dialysis required, reduce to 5 mg daily and give post-dialysis.</td>
<td></td>
</tr>
</tbody>
</table>

*Patients with a CrCl < 50 mL/min were excluded from the pivotal Phase 3 trial.

**Dosage in the Elderly**

There were no differences in effectiveness of carfilzomib, in combination with lenalidomide and dexamethasone, in any of the studied age groups. Patients aged 65 years or more, especially those more than 75 years, had more serious adverse events, including cardiac events.
F - Adverse Effects

Refer to carfilzomib, lenalidomide and dexamethasone drug monograph(s) for additional details of adverse effects

<table>
<thead>
<tr>
<th>Common (25-49%)</th>
<th>Less common (10-24%)</th>
<th>Uncommon (&lt; 10%), but may be severe or life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatigue</td>
<td>• Dizziness</td>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>• Edema - limbs</td>
<td>• GI perforation</td>
</tr>
<tr>
<td>• Infusion-related reactions</td>
<td>• Rash (may be severe)</td>
<td>• Renal failure</td>
</tr>
<tr>
<td>• Abnormal electrolyte(s)</td>
<td>• Constipation</td>
<td>• Peripheral neuropathy</td>
</tr>
<tr>
<td>• Myelosuppression ± infection (includes atypical, viral reactivation), bleeding (may be severe)</td>
<td>• Insomnia</td>
<td>• Cardiotoxicity</td>
</tr>
<tr>
<td>• Musculoskeletal pain (including spasms)</td>
<td>• Dyspepsia</td>
<td>• Hypotension</td>
</tr>
<tr>
<td>• Cough, dyspnea</td>
<td>• Hypertension (may be severe)</td>
<td>• Tumor lysis syndrome</td>
</tr>
<tr>
<td>• Fever</td>
<td>• Dysgeusia</td>
<td>• Arterial thromboembolism</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Venous thromboembolism (may be severe)</td>
<td>• Adult respiratory distress syndrome (ARDS)</td>
</tr>
<tr>
<td>• Nausea, vomiting</td>
<td>• Hyperglycemia</td>
<td>• Cholecystitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hemorrhage</td>
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<tr>
<td></td>
<td></td>
<td>• Pneumonitis</td>
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<td></td>
<td></td>
<td>• Pulmonary hypertension</td>
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<tr>
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<td></td>
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<td>• ↑ LFTs</td>
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<tr>
<td></td>
<td></td>
<td>• Rhabdomyolysis</td>
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<td></td>
<td></td>
<td>• PRES</td>
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<tr>
<td></td>
<td></td>
<td>• Increased QTc</td>
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<tr>
<td></td>
<td></td>
<td>• Atrial fibrillation</td>
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<tr>
<td></td>
<td></td>
<td>• Blurred vision,</td>
</tr>
</tbody>
</table>
G - Interactions

Refer to carfilzomib, lenalidomide and dexamethasone drug monograph(s) for additional details

- It is unknown whether carfilzomib is an inducer of CYP1A2, 2C8, 2C9, 2C19 and 2B6. Caution should be observed when combined with products which are substrates of these enzymes, including oral contraceptives.
- Carfilzomib dose not induce, but may inhibit, CYP3A4/5.
- Caution with P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron) and monitor digoxin levels.
- Caution and consider non-hormonal method(s) of contraception as use of oral contraceptives or other hormonal methods of contraception may increase risk of blood clots. Oral contraceptives may also have reduced efficacy.
- Lenalidomide is not a substrate, inhibitor or inducer of CYP450; co-administration with substrates or inhibitors of this enzyme is unlikely to result in significant drug interactions.
- Lenalidomide increases risk of thromboembolic events and would have an additive effect if coadministered with other thromboembolic agents.

H - Drug Administration and Special Precautions

Refer to carfilzomib, lenalidomide and dexamethasone drug monograph(s) for additional details

**Administration:**

**carfilzomib**

- carfilzomib dosed at 27 mg/m$^2$ should be infused over at least 10 minutes
- may further dilute dose in 50-100 mL D5W. Do not dilute in NS for IV administration.
- carfilzomib should not be administered as an IV bolus
- flush line before and after carfilzomib administration with NS or D5W
lenalidomide

- oral self-administration; swallow capsules whole; they should not be broken, chewed, or opened. Do not extensively handle the capsules
- give capsules preferably with water, either with or without food. Do not remove from blister packs until ready to take the dose
- females who could become pregnant, or who plan to become pregnant can handle lenalidomide capsules if they are using latex gloves

dexamethasone

- oral self-administration or may be given by IV route on carfilzomib clinic days
- give tablets with food, preferably in the morning

Contraindications:

- patients who have a hypersensitivity to these drugs or any of their components
- women at risk of being pregnant and male patients who do not comply with contraception requirements (see Pregnancy section in lenalidomide drug monograph for additional details)

Other Warnings/Precautions:

carfilzomib

- use with caution in patients on a controlled sodium diet. Each mL contains 0.3 mmols (7 mg) of sodium
- the risk of heart failure is increased in elderly patients (≥ 75 years). Patients with NYHA Class III/IV heart failure, recent MI, conduction abnormalities, angina or arrhythmias uncontrolled by medications were not eligible for carfilzomib-based clinical trials. These patients may be at greater risk of cardiac complications and should have their medical management optimized, including hypertension, prior to starting treatment with carfilzomib and monitored closely throughout
- caution with driving or using machinery as fatigue, dizziness and a drop in blood pressure may occur with treatment

lenalidomide

- contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption
- use with caution and consider venous thromboembolism prophylaxis when used in combination with corticosteroids or thrombogenic agents, such as hormones and erythropoietin (see Adverse Effects section in lenalidomide drug monograph for additional details)
- exercise caution in patients with risk factors for arterial thromboembolism (e.g. hypertension and hyperlipidemia), or risk factors for atrial fibrillation (e.g. electrolyte abnormalities, pre-existing heart disease, hypertension, infection)
- use with caution in patients with high tumour burden; monitor closely and use appropriate precautions for tumour lysis syndrome
- use with caution and monitor closely in patients with previous viral infections such as HBV and
I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- Blood pressure; Baseline and before each treatment
- CBC with differential; Baseline and before each treatment week
- Electrolytes, including potassium; Baseline and before each cycle
- Liver and renal function tests; Baseline and before each cycle
- Thyroid function tests; Baseline and as clinically indicated
- Specific to lenalidomide: RevAid requirements regarding pregnancy tests for women of child-bearing potential; Before starting and as indicated per RevAid
- Clinical toxicity assessment and grading of cardiac, gastrointestinal and respiratory symptoms, rash, fatigue, infection (including viral reactivation), bleeding, tumour lysis syndrome, arterial and venous thromboembolism; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Blood glucose levels; Baseline and regular
- ECG; Baseline; repeat if arrhythmia suspected
- INR in patients receiving warfarin; Baseline and as clinically indicated
- LVEF assessment (especially in patients ≥ 75 years, or those at greater risk for cardiac complications); Baseline and as clinically indicated

J - Administrative Information

lenalidomide, dexamethasone po - Outpatient prescription for home administration

Approximate Patient Visit

- First cycle: 12 hours (includes pre- and post-IV hydration); Cycles 2 to 12: 3 hours (if no IV hydration); Cycles 13 to 18: 2 hours
Pharmacy Workload (average time per visit) 19.850 minutes
Nursing Workload (average time per visit) 42.417 minutes

K - References

Carfilzomib, lenalidomide drug monographs, Cancer Care Ontario.


May 2018 Updated rationale and uses and supplementary public funding sections; removed "unfunded" from lenalidomide and carfilzomib

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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